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Chronic hepatitis B prevalence among foreign-born and US-born adults in the United States, 1999-2016

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Abbreviations: Anti-HBc: hepatitis B core antibody; anti-HBs: hepatitis B surface antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CHB: chronic hepatitis B; CI: confidence intervals; USFLI: United States fatty liver index; HBsAg: hepatitis B surface antigen; HBV: Hepatitis B virus; HMO: health maintenance organization; NHANES: National Health and Nutrition Examination Survey; U.S.: United States

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Abstract (243/275)

Hepatitis B virus (HBV) infection remains a major global health problem, exacerbated by poor linkage to care. We aimed to determine the prevalence of HBV infection, exposure, self-reported vaccination, vaccine-induced immunity, disease awareness, and treatment in the United States (U.S.) by birthplace and race/ethnicity during 1999-2016. 47,628 adult participants in the National Health and Nutrition Examination Survey completed HBV core antibody (anti-HBc) and surface antigen (HBsAg) tests and 47,618 adults completed HBV surface antibody (anti-HBs) and anti-HBc tests and were included in the analysis. HBV infection was defined by positive HBsAg and past exposure by positive anti-HBc. Vaccine-mediated immunity was defined by positive anti-HBs and negative anti-HBc. No significant change in the prevalence of HBV infection was observed between 1999-2016 (P=0.442), affecting 0.35% (95% CI: 0.28-0.45) or 0.84 million adults. In contrast, a significant decrease in HBV exposure and increase in vaccine-mediated immunity was observed. U.S. born had significantly lower prevalence of HBV infection and exposure as well as higher prevalence of vaccine-mediated immunity and self-

reported vaccination than foreign born. Prevalence of HBV infection was highest in non-Hispanic Asians in both foreign- (3.85%, 95% CI: 2.97-4.97) and U.S.-born (0.79%, 95% CI: 0.17-3.59) persons during 2011-2016. Among infected persons, liver disease awareness was only 15.19%, and treatment rate was only 4.60%.

Conclusion: This study revealed disparities of HBV infection among ethnic/racial groups and between U.S.-born and foreign-born persons. Awareness of liver disease and treatment rate among infected persons was dismal.

Introduction

Hepatitis B virus (HBV) infection continues to be a global health threat and a leading cause of cirrhosis and primary liver cancer, globally affecting approximately 257 million people according to the World Health Organization in 2015 and 292 million people according to the Polaris Observatory in 2016(1, 2). In the United States (U.S.), prior analyses of non-institutionalized persons without adequate sampling of racial/ethnic minorities estimated there was a total of 847,000 persons with HBV infection in 2011-2012 (3). However, the total burden has been estimated to be as high as 2.2 million in analyses that accounted for HBV prevalence in high-risk U.S.-born and immigrant populations (4).

Poor disease awareness and linkage to care may contribute to the high disease burden of HBV (2-4). The Racial and Ethnic Approaches to Community Health (REACH) study, which surveyed 28 minority communities across the U.S, reported poor awareness and linkage to care among ethnic minorities (5). Studies from community and academic medical centers have also shown suboptimal evaluation and under-treatment even among those linked to care (6-9).

Non-Hispanic Asians are an important ethnic minority group with probably the highest disease burden from HBV in the U.S.; yet prior iterations of one of the largest national programs for the study of the health of adults and children in the U.S., the National Health and Nutrition Examination Survey (NHANES), did not adequately sample non-Hispanic Asian. To remedy this

deficiency, Asians have been oversampled since 2011 to provide more nationally representative data (10).

Therefore, we aimed to use the NHANES database from 1999 to 2016 to provide population estimates for HBV infection, exposure, immunity, liver disease awareness, liver disease severity, and treatment rates for all major racial/ethnic groups including Asian Americans and examine the impact of birthplace (U.S. vs. foreign born).

Methods

Data source and study population

Our study utilized data from NHANES 1999-2016. Details of survey design and laboratory methods can be found in **Supplemental Appendix 1**. All participants provided written informed consent prior to participation in NHANES. To determine the prevalence of HBV exposure and infection, we included adult participants aged 18 years and older who had completed hepatitis B core antibody (anti-HBc) and hepatitis B surface antigen (HBsAg) testing. For self-reported vaccination history, we included patients who answered questions regarding vaccination history in NHANES questionnaire. For vaccine-induced immunity, we identified participants who had both hepatitis B surface antibody (anti-HBs) and anti-HBc testing. Participant birthplace was based on self-reporting.

Data extraction and variable definition

Analysis of HBV prevalence, exposure, serologic evidence of vaccine-mediated immunity and self-reported vaccination history

We defined HBV infection as seropositivity for HBsAg and exposure to HBV as seropositivity for anti-HBc. Serologic evidence of vaccine-mediated immunity was defined as seropositivity for anti-HBs and seronegativity for anti-HBc. Those who were anti-HBs and anti-HBc reactive were considered as having immunity by prior exposure.

For history of self-reported vaccination, we extracted data on participant response to the questionnaire regarding history of vaccination. Participants who responded “yes, all three doses”

to the question "have you ever received the 3-dose series of the hepatitis B vaccine?" were defined as having history of vaccination.

Analysis of HBV disease severity, concurrent fatty liver, general healthcare utilization, awareness of liver disease, and treatment rate for HBV infection

We evaluated liver disease severity by liver enzymes (AST [aspartate aminotransferase] and ALT [alanine aminotransferase]), and FIB-4 score (11). The formula for FIB-4 score is (age*AST level)/(platelet count*$ALT^{1/2}$). We also extracted relevant laboratory data to calculate the United States Fatty Liver Index (USFLI) to identify patients with concurrent fatty liver (12). Participants with a USFLI > 30 were considered to have fatty liver.

Awareness of having a liver disease, general healthcare utilization, and rate of treatment for HBV infection were assessed through the NHANES questionnaire. To evaluate participant awareness of liver disease, we extracted the response to the survey question "Has a doctor or other health professional ever told you that you had any kind of liver condition?" This question is not specific for HBV infection but participants who were aware of HBV infection would most likely be aware that they had a liver condition. The answer to this question is binary – either "yes" or "no."

For participant healthcare utilization within the past 12 months, we extracted the response to the survey question "During the past 12 months, how many times have you seen a doctor or other healthcare professional about your health at a doctor's office, a clinic, hospital emergency room, at home or some other place?" Finally, we estimated the rate of anti-HBV treatment based on NHANES interviewer review of all prescribed medication containers. If no container was available at the time of interview, the interviewer asked the participant to verbally report the name of the medication. A list of HBV antiviral drugs recorded in NHANES can be found in **Supplemental Table 1**.

Analysis by race/ethnicity and birthplace

Birthplace of each subject was categorized as U.S.-born or foreign-born. Participants were asked to select one of the six racial/ethnic groups that fits them best: non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, non-Hispanic Asian, and other-multiracial. Data on

non-Hispanic Asians were only available for 2011 to 2016 survey. Therefore, race/ethnicity specific analyses only included data from NHANES 2011-2016.

Analysis for time trends

Trends analyses were conducted for 1999-2016. In addition, subgroup analyses were conducted by combining data for three 6-year periods: 1999-2004, 2005-2010, and 2011-2016.

Statistical analyses

Adjusted prevalence estimates of HBV infection, HBV exposure, self-reported vaccination history and hepatitis B vaccine-mediated immunity were calculated for each NHANES survey cycle, from 1999 to 2016. Trends analyses were conducted using logistic regression, with NHANES survey cycle as the dependent variable. Race/ethnic specific estimates for HBV infection, HBV exposure, self-reported vaccination history and hepatitis B vaccine-mediated immunity were calculated using data from 2011 to 2016, as NHANES only began oversampling for non-Hispanic Asians from 2011.

Population estimates for HBV infection, exposure, and immunity in the general population were calculated using NHANES data from the most recent cycles 2011-2016, which has adequate sample size for subanalyses on race/ethnicity specific population estimates. In order to calculate the population estimates, adjusted prevalence estimates were multiplied by population totals from the American Community Survey of the U.S. Census Bureau averaged over their respective time periods.

Univariate and multivariate logistic regression were used to estimate odds ratios relating various participant characteristics to disease awareness, and multinomial logistic regression was used to estimate risk ratios relating participant characteristics to healthcare utilization. All variables that had a $p<0.10$ in stepwise forward logistic regression, or those that were clinically relevant were included in the model.

A two-tailed p-value of <0.05 was considered to be statistically significant. Weighted analyses were performed using STATA 15.1 (Stata Corporation, College Station, TX, USA), which

allows appropriate utilization of the NHANES survey weights to project the results of the analysis to the noninstitutionalized, general population of the U.S.

Results:

Study population

As shown in **Figure 1**, of the 92,062 participants in NHANES between 1999 and 2016, we excluded 38,714 younger than 18 years. We then separated the NHANES participants into 3 groups based on completion of HBsAg, anti-HBc, and both anti-HBc and anti-HBs tests. Among the 53,348 participants aged 18 years or older, 89.31% (n=47,650) were tested for both HBsAg and anti-HBc, all but 10 of these were also tested for anti-HBs. Twenty-two persons were excluded due to missing birthplace data. In total, we included 35,263 U.S.-born and 12,365 foreign-born persons who completed HBsAg testing and anti-HBc testing and 35,255 U.S.-born and 12,363 foreign-born persons in the study analyses.

Prevalence of HBV infection, exposure, self-reported vaccination history, and serologic evidence of vaccine-mediated immunity

Overall analysis and analysis by birthplace

Overall, 232 (0.49%) persons included in the study tested HBsAg positive; of whom, 88 were U.S. born (37.90%) and 144 were foreign born (62.10%). During 1999-2016, there was no significant change in the prevalence of HBV infection in the general U.S. population, with an adjusted overall prevalence of 0.31% (95% CI: 0.20-0.50) during 1999-2000 and 0.29% (95% CI: 0.18-0.47) during 2015-2016 (p=0.442) (**Figure 2A**). Since 2011, when oversampling of Asians was initiated, HBV prevalence was higher among foreign-born vs. U.S.-born persons. In addition, despite variations in NHANES cycles, there were no statistically significant changes in HBV prevalence for either U.S.-born (p=0.347) or foreign-born (p=0.270) groups **(Figure 2B, Table 1).**

We observed a significant decrease in the prevalence of HBV exposure from 5.80% (95% CI: 4.51-7.42) during 1999-2000 to 4.69% (95% CI: 3.89-5.65) during 2015-2016 (p=0.014) (**Figure 2C**). However, on subanalysis by birthplace, this decrease was observed only in U.S.-born

persons from 4.22% (95% CI: 3.31-5.36) in 1999-2000 to 2.66% (95% CI: 2.13-3.30) in 2015-2016 (p<0.001), but not in the foreign-born group (p=0.437) **(Figure 2D, Supplemental Table 2)**.

During 1999-2016, the prevalence of vaccine-mediated immunity increased significantly from 10.8% (95% CI: 9.8-12.0) in 1999-2000 to 23.1% (95% CI: 20.8-25.6) 2015-2016 (p<0.001) (**Figure 2A and Figure 2C**) overall, with increases in both the U.S.-born from 11.3% [95% CI: 10.2-12.6] to 23.6%, [95% CI: 21.1-26.4]; p<0.001) and foreign-born groups from 8.5%. [95% CI: 6.26-11.3] to 21.0%, [95% CI: 17.9-24.5]; p<0.001).

Out of the whole study population of 47,621, a total of 33,867 participants (71.12%) did not have complete vaccination, with 32,457 participants (67.22%) responding "No" to any vaccination and 1,410 (3.07%) to "less than 3 doses". We observed a discrepancy in the prevalence of self-reported vaccination history and vaccine-mediated immunity by serologic results (anti-HBs reactive but anti-HBc negative). For example, in 2011-2016, 36.79% (95% CI: 35.56-38.04) of participants reported having completed the 3-dose hepatitis B vaccine series, but serologic evidence of vaccine-mediated immunity was observed in only 23.11% (95% CI: 21.96-24.30) (**Supplemental Tables 3 and 4**).

Analysis by age, race/ethnicity, and birthplace among cohorts studied in 2011-2016

The prevalence of HBV infection was lowest among the younger age groups and highest among the older age groups, with the exception of non-Hispanic blacks whose HBV prevalence did not vary with age (0.54%-0.75%, p=0.905) (**Figure 3**). Among non-Hispanic blacks, HBV prevalence was generally higher in U.S.-born than foreign-born persons except for those in the 18-34 age group (**Figure 3, third panel**). In contrast, among non-Hispanic Asians, the vast majority of persons with HBV infection were foreign-born and this was true across all age groups (**Figure 3, sixth panel**).

The prevalence of HBV exposure as well as immunity through prior exposure increased with age (**Figure 4**). As expected, the prevalence of serologic evidence of vaccine-mediated immunity was highest in young adults and lower in older adults (**Figure 4, gray bar**). Additional

information on race/ethnicity-specific prevalence of HBV infection, exposure, and vaccine-mediated immunity stratified by various demographic variables in foreign-born and U.S-born participants can be found in **Supplemental Tables 5 and 6**, respectively.

Population estimates of HBV infection, exposure, and serologic evidence of vaccine-mediated immunity

Population level analyses for the most recent time period 2011-2016 estimated a total of 0.84 million (95% CI: 0.67-1.07 million) persons with HBV infection, 11.10 million (95% CI: 9.91-12.44 million) persons with prior exposure to HBV, and 54.98 million (95% CI: 52.19-57.87 million) persons with vaccine-mediated immunity among the general non-institutionalized U.S. population (**Supplemental Table 7**). **Supplemental Tables 8, 9, and 10** described the race/ethnic-specific population estimates for the overall population, the U.S-born population, and the foreign-born population, respectively.

Analysis of the HBV-infected cohort: demography, disease severity, general healthcare utilization, disease awareness, and treatment rate

Based on data of the 232 persons with HBV infection, population estimates on various demographic and clinical characteristics of the population infected with HBV were calculated and described in **Table 2**. The mean age was 46.50 ± 15.9, 61.29% was male, and 56.80% were foreign-born. Among the foreign-born, non-Hispanic Asian made up the largest group (49.84%), followed by non-Hispanic black (25.55%). Among U.S.-born persons with HBV infection, non-Hispanic white group made up the largest group (49.15%) followed by non-Hispanic black (45.53%).

While foreign-born persons carried the majority of the HBV disease burden, U.S.-born persons with HBV infection were more likely to have elevated aminotransferases (ALT or AST >2X upper limit of normal (ULN)) compared to foreign born persons (13.20% vs. 3.21%, p=0.008). There was also a trend for a higher prevalence of advanced liver fibrosis in the U.S.-born group (6.28% FIB-4 > 3.25 vs. 3.04%, p=0.070). U.S.-born persons were also older and had a higher rate of significant alcohol use defined as >1 drink/day for women and >2 drink/day for men

(37.7% vs. 22.7%, *p*=0.067). However, there was no significant difference in the prevalence of fatty liver between the U.S.-born vs. foreign-born groups as assessed by the USFLI (26.72% vs. 20.74%, *p*=0.484).

Population estimates for liver disease awareness rates was based on data from the 191 persons who answered the survey question about having been told of a liver condition. Disease awareness rate was very low overall with only 15.19% of persons who tested HBsAg positive reporting having been told they had a liver condition by a doctor or other health professionals. There were no statistically significant differences in the liver disease awareness rate between U.S.-born and foreign-born persons with HBV infection (*p*=0.814) (**Table 2**). In sensitivity analysis for disease awareness by time period, we found that there was no significant difference in the awareness rate among the 71 infected persons in 1999-2006 compared to the 120 persons in 2007-2016 (16.90%, 95%CI 8.77-30.09 vs. 13.80, 95%CI 8.39-21.85, *p*=0.61). Notably, the majority of both U.S.-born (96.60%) and foreign-born (65.70%) participants with HBV infection reported having received care at least once in the 12 months preceding the survey. In multivariable logistic regression (**Supplemental Table 12**), after controlling for age, gender, insurance status, race/ethnicity, birthplace, poverty, and educational levels, the only independent predictor for increased disease awareness among infected persons was having one or more healthcare visits (versus none) in the previous 12 months (adjusted odds ratio=5.22, *p*=0.042). In an alternative model controlling for the same variables but with further breakdown of the number of healthcare visits in 12 months (1, 2-3, 4 or more versus none), we observed that having only one visit per year was not a statistically significant predictor for higher likelihood of disease awareness (adjusted odds ratio=3.26, *p*=0.175), while there was a trend with 2-3 visits a year (adjusted odds ratio=5.24, *p*=0.109) and having ≥4 healthcare visits in the past year was a statistically significant predictor (adjusted odds ratio= 19.00, *p*=0.004). In multinomial logistic regression, older persons, female, U.S.-born, insured, and more educated persons were more likely to visit a healthcare facility in the previous 12 months (**Supplemental Table 11**).

Of the 28 participants infected with HBV who were aware of their liver condition, 8 (26.26%) had received or were receiving antiviral treatment, giving an overall treatment rate of roughly

5% among all infected persons. Data for subanalysis by birthplace were shown in **Table 2**, but the sample sizes for subgroups were very small.

Supplemental figure 1 shows the population estimates for HBV infection, awareness, overall treatment, and treatment among those aware of infection in this NHANES cohort, 1999-2016.

Discussion

Using the NHANES database, we determined the prevalence of HBV infection in the general U.S. adult population from 1999-2016 remained stable, while the prevalence of HBV exposure significantly decreased, and the prevalence of vaccine-mediated immunity significantly increased during this period. Based on the most recent survey in 2015-2016, the prevalence of HBV infection was 0.29% which equated to 0.71 million persons with HBV infection among the noninstitutionalized, general U.S. population. Overall, U.S.-born and younger persons showed a lower prevalence of HBV infection and exposure as well as a higher prevalence of vaccine-mediated immunity and self-reported vaccination than foreign-born and older persons. There was also a trend for higher rate of advanced fibrosis in U.S.-born HBV-infected persons compared to the foreign-born group, and this can be due to the older age and higher rate of significant alcohol use among the U.S.-born cohort.

A very encouraging finding for the U.S.-born population was the positive effect that the multifaceted efforts to reduce HBV infection (screening of pregnant women, universal infant and catch-up vaccinations, and screening of blood supply (13-15), had in decreasing HBV exposure. However, despite the progress of vaccination coverage in the U.S., we found over 70% of the general adult population did not have serological evidence of vaccine-mediated immunity. Our results are also in line with recent reports that approximately 64 million U.S. persons considered to be high-risk by the Centers for Disease Control and Prevention criteria still had undetectable immunity against HBV in 2013-2014 (69.4%)(16) suggesting that while these efforts are effective, efforts may need to be specifically targeted to those at the highest risk for HBV (foreign born, non- Hispanic Asian, adults with high risk behaviors) to bring about a substantial decrease in HBV exposure.

Among U.S.-born persons, non-Hispanic blacks who were male, 50-64 years old, heavy drinkers, on government health care insurance were found to have the highest prevalence (0.54%) and the highest prevalence of exposure on the population level (8.35%). Such a finding may be due to a lower use of health care and thus a lower chance of HBV vaccination. (17, 18) Together, these are important findings as Asians and blacks with chronic hepatitis B are known to have an 11-fold and 7-fold higher risk for developing HCC than whites, respectively (17). Furthermore, a recent study found poorer survival of African American patients with HCC compared to white patients (19). Therefore, more efforts are needed to screen these high- risk persons for HBV, to enter them into an HCC surveillance program using culturally appropriate approaches and to consider them for treatment to prevent long-term complications such as HCC (18). Such a recommendation would also be in line with the report from a US HBV screening surveillance study sponsored by the Centers for Disease Control and Prevention in which the investigators concluded that persons born in highly- HBV endemic countries (China, Vietnam, Somalia, Myanmar, and Laos) should be considered high risk for HBV and screened appropriately(20). Furthermore, we would suggest that both providers and at-risk populations need education and that the use of alerts in electronic health records or a clinical check list with place of birth should be used to improve HBV screening/diagnosis and treatment (19-21).

The current study also noted that, among HBV-infected persons, only 15% of patients were aware of having a liver disease and only 5% received antiviral therapy; however, among those that were aware almost 25% did receive treatment. We recognize that the survey question was not specific for HBV infection, and it is possible that some participants who did not have symptoms of liver disease might be aware they were infected but did not consider themselves to have a liver disease or did not remember being told (recall bias). We also recognize due to the lack of HBV DNA and HBeAg data in NHANES, we were not able to identify patients who met indications for antiviral therapy so the treatment rate must be interpreted with caution requiring further study. In addition, our results may not be generalizable given our small sample size (4, 21).

In addition to the study limitations noted above, we recognize that we could not differentiate between acute and chronic HBV infection since we had HBsAg result from only one time point, though it is likely that the vast majority of persons who tested positive in population surveys have a chronic infection (22). Moreover, the absence of serologic evidence of vaccine-mediated immunity may not mean lack of immunity as some might have had prior vaccination with loss of anti-HBs over time, and these persons may remain protected upon exposure (23, 24). Additionally, this study likely underestimates the true prevalence of HBV infection in the U.S., as NHANES does not sample for several high-risk populations such as the homeless and incarcerated. Finally, treatment options for hepatitis B in earlier years were limited, though disease awareness rates did not improve in recent years.

In conclusion, the prevalence of HBV infection has remained relatively stable during 1999-2016 in the civilian population of the U.S. at 0.35% with an estimated 0.84 million infected persons during 2011-2016. There are wide variations in prevalence of HBV infection and exposure by age, race/ethnicity, and birthplace. The majority of HBV burden occurred in foreign-born persons, with non-Hispanic Asian having the highest prevalence (3.30%). Meanwhile, non-Hispanic blacks had the highest prevalence among U.S.-born persons (0.54%). Among persons with HBV infection, awareness of having a liver condition and treatment rate were low. To achieve the goal of the Department of Health and Human Services to increase the diagnosis rate from one-third to two-thirds of persons with chronic HBV by 2020 (25) and the elimination of HBV by 2030, more effort is needed to improve screening and disease awareness among providers and high risk groups for HBV infection so as to provide vaccination to those who remain unvaccinated and treatment to those who require treatment(16).

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Table 1. Prevalence of HBV infection (positive HBsAg), 1999-2016

	1999-2004		2005-2010		2011-2016		Trends analysis
Characteristics	**Sample Size**	**Adjusted % (95% CI)**	**Sample Size**	**Adjusted % (95% CI)**	**Sample Size**	**Adjusted % (95% CI)**	**P-value**
Overall	14,876	0.32 (0.24-0.43)	16,601	0.35 (0.25-0.50)	16,148	0.35 (0.28-0.45)	**0.602**
Sex							
Male	7,121	0.40 (0.28-0.58)	8,094	0.51 (0.33-0.78)	7,835	0.40 (0.28-0.57)	0.926
Female	7,758	0.24 (0.14-0.43)	8,094	0.21 (0.13-0.32)	8,507	0.31 (0.23-0.42)	0.408
Age groups (Years)							
18-34	5,182	0.35 (0.20-0.64)	5,037	0.29 (0.14-0.58)	4,764	0.30 (0.19-0.47)	0.641
35-49	3,346	0.33 (0.19-0.58)	4,031	0.32 (0.17-0.60)	3,927	0.37 (0.25-0.57)	0.710
50-64	2,804	0.36 (0.20-0.65)	3,731	0.60 (0.39-0.94)	3,981	0.41 (0.26-0.64)	0.898
65+	3,547	0.18 (0.08-0.45)	3,802	0.16 (0.08-0.34)	3,476	0.35 (0.17-0.70)	0.241
Birthplace							
U.S.	11,528	0.17 (0.12-0.25)	12,503	0.21 (0.13-0.33)	11,232	0.15 (0.10-0.24)	0.706
Foreign	3,351	1.16 (0.75-1.80)	4,098	1.07 (0.62-1.85)	4,916	1.28 (0.95-1.73)	0.675
Race/Ethnicity							
NH-white	7,162	0.08 (0.04-0.17)	7,894	0.18 (0.11-0.31)	6,060	0.11 (0.05-0.24)	0.633
NH-black	2,917	1.05 (0.64-1.72)	3,327	0.78 (0.48-1.24)	3,571	0.69 (0.45-1.04)	0.201
Mexican	3,596	0.03 (0.01-0.15)	3,204	0.06 (0.02-0.23)	2,298	0.17 (0.06-0.50)	0.092

American							
Hispanic	665	0	1,404	0.24 (0.08-0.70)	1,729	0.06 (0.01-0.37)	0.390
NH-Asian	0	N/A	0	N/A	1,964	3.41 (2.64-4.39)	N/A
Other	539	3.17 (1.95-5.12)	772	2.01 (1.06-3.79)	526	0.40 (0.12-1.30)	0.002
Education Level (Age 20+)							
<High school	4,304	0.59 (0.36-0.98)	4,526	0.36 (0.20-0.64)	3,480	0.49 (0.31-0.80)	0.571
High school	6,555	0.25 (0.17-0.38)	7,934	0.35 (0.22-0.57)	8,008	0.32 (0.24-0.45)	0.331
≥College	2,454	0.28 (0.11-0.68)	3,072	0.37 (0.18-0.75)	3,847	0.32 (0.20-0.52)	0.802
Birthplace and Race/Ethnicity							
U.S.	**11,528**	**0.17 (0.12-0.25)**	**12,503**	**0.21 (0.13-0.33)**	**11,232**	**0.15 (0.10-0.24)**	**0.706**
NH white	6,785	0.06 (0.03-0.15)	7,478	0.14 (0.08-0.24)	5,799	0.08 (0.03-0.22)	0.700
NH black	2,638	0.76 (0.46-1.25)	3,018	0.54 (0.30-0.97)	3,153	0.52 (0.32-0.85)	0.312
Mexican	1,611	0	1,279	0.09 (0.01-0.67)	1,032	0.14 (0.03-0.61)	0.207
Hispanic	227	0	415	0.37 (0.08-1.68)	530	0	0.831
NH Asian	0	N/A	0	N/A	291	0.79 (0.17-3.59)	N/A
Other	267	1.39 (0.35-5.38)	313	0.91 (0.22-3.65)	427	0.46 (0.14-1.54)	0.255
Foreign	**3,351**	**1.16 (0.75-1.80)**	**4,098**	**1.07 (0.62-1.85)**	**4,916**	**1.28 (0.95-1.73)**	**0.675**
NH white	377	0.38 (0.12-1.17)	416	1.06 (0.35-3.17)	261	0.64 (0.14-2.93)	0.556
NH black	279	3.84 (1.86-7.76)	309	2.95 (1.13-7.46)	418	1.94 (1.13-3.30)	0.138
Mexican	1,985	0.05 (0.01-0.27)	1,925	0.04 (0.01-0.17)	1,266	0.19 (0.04-0.88)	0.247
Hispanic	438	0	989	0.18 (0.03-0.93)	1,199	0.09 (0.01-0.53)	0.349
NH Asian	0	N/A	0	N/A	1,673	3.85 (2.97-4.97)	N/A
Other	272	4.72 (2.59-8.46)	459	2.70 (1.33-5.43)	99	N/A	0.068
Insured	**11,596**	**0.30 (0.20-0.44)**	**12,542**	**0.33 (0.22-0.49)**	**12,737**	**0.33 (0.26-0.41)**	**0.699**

Private	6,757	0.24 (0.15-0.37)	6,806	0.30 (0.17-0.54)	6,575	0.28 (0.20-0.38)	0.593
Government	4,741	0.40 (0.23-0.71)	5,678	0.38 (0.24-0.61)	6,042	0.41 (0.28-0.61)	0.902
Uninsured	3,100	0.44 (0.28-0.70)	4,041	0.46 (0.24-0.87)	3,386	0.50 (0.29-0.86)	0.758
Pregnant at time of survey	**801**	**0.06 (0.01-0.41)**	**450**	**0.82 (0.21-3.21)**	**169**	**0**	**0.527**
Poverty-income ratio							
<1	2,778	0.50 (0.24-1.03)	3,289	0.37 (0.17-0.78)	3,509	0.51 (0.32-0.82)	0.896
≥1	10,835	0.27 (0.19-0.38)	12,024	0.34 (0.23-0.50)	11,248	0.31 (0.22-0.42)	0.575
Military Veteran	2039	0.15 (0.07-0.31)	2070	0.36 (0.13-0.98)	1482	0.18 (0.07-0.42)	0.628
Heavy drinker*							
Male	1,946	0.35 (0.16-0.75)	2,443	0.46 (0.21-0.97)	2455	0.26 (0.16-0.43)	0.516
Female	1,796	0.12 (0.34-0.39)	2,261	0.15 (0.05-0.47)	2332	0.14 (0.06-0.33)	0.828
FIB-4 score							
<1.45	11,932	0.29 (0.21-0.42)	12,675	0.32 (0.21-0.48)	11,845	0.27 (0.20-0.37)	0.745
1.45-3.25	2,643	0.40 (0.20-0.80)	3,413	0.52 (0.30-0.89)	3,788	0.60 (0.39-0.91)	0.324
>3.25	304	1.11 (0.41-3.01)	513	0.36 (0.05-2.67)	515	0.70 (0.42-1.18)	0.586
ALT or AST >2X ULN[#]	570	1.54 (0.64-3.65)	621	0.68 (0.13-3.39)	554	2.48 (1.26-4.83)	0.734
NAFLD[##]	2,202	0.18 (0.06-0.53)	2,583	0.29 90.12-0.66)	2,365	0.34 (0.17-0.69)	0.334

*Heavy drinker defined as: >2 drinks/day for men or >1 drink/day for women

[#]AST ULN: 40 U/L, ALT ULN: 35 U/L for males 25 U/L for females

[##]NAFLD defined by USFLI, USFLI ≥30

Table 2: Characteristics of persons with HBV infection (positive HBsAg)

Variable	Total HBV (n=232)*	U.S. born (n=88)*	Foreign born (n=144)*	P-value[#]
Age (mean ± SD)	**46.50** ± 15.90	50.82 ± 14.28	43.2 ± 16.29	0.001
Male	61.29 (53.20-68.81)	61.82 (48.54-73.54)	60.90 (50.3-70.6)	0.913
Race/ethnicity				**<0.001**
Non-Hispanic White	33.96 (24.81-44.50)	49.15 (36.09-62.32)	18.30 (9.60-32.08)	
Non-Hispanic Black	35.70 (27.55-44.75)	45.53 (33.05-58.59)	25.55 (17.42-35.83)	
Mexican American	3.06 (1.26-7.27)	2.34 (0.71-7.40)	3.81 (1.17-11.7)	
Other Hispanic	1.90 (0.68-5.16)	1.32 (0.27-6.17)	2.50 (0.66-9.01)	
Non-Hispanic Asian	25.38 (19.03-32.99)	1.66 (0.37-7.20)	49.84 (37.65-62.05)	
Awareness of liver disease	**15.19** (10.11-22.19)	14.40 (7.30-26.44)	15.89 (9.44-25.53)	0.814
Treated among aware	**26.26 (10.65-51.53)**	49.49 (17.76-81.64)	7.68 (2.01-25.28)	0.021
Treated among all infected	**4.60** (2.02-10.16)	7.03 (2.43-18.67)	2.54 (0.87-7.20)	0.158
Income:poverty ratio >1	**79.17 (71.23-85.37)**	82.12 (70.28-89.92)	76.67 (65.97-84.79)	0.416
Treated among income:poverty ratio >1	**4.77 (1.72 – 12.50)**	8.07 (2.44-23.53)	1.40 (0.33-5.84)	0.040
Insurance	**75.35 (67.72-81.68)**	83.37 (72.22-90.62)	69.25 (57.68-78.82)	0.065
Treated among insured	**6.12 (2.69-13.33)**	8.39 (2.94-21.70)	3.74 (1.21-10.99)	0.278
FIB-4 >3.25	4.44 (2.51-7.76)	6.28 (2.62-14.32)	3.04 (1.81-5.05)	0.070
% with NAFLD[##]	23.45 (14.69-35.26)	26.72 (13.16-46.72)	20.74 (12.55-32.30)	0.484
ALT or AST >2X ULN**	7.54 (4.16-13.29)	13.20 (6.52-24.90)	3.21 (1.30-7.70)	0.008
Times received healthcare over past year				**<0.001**
0	21.01 (15.05-28.54)	3.40 (1.34-8.35)	34.30 (24.8-45.18)	

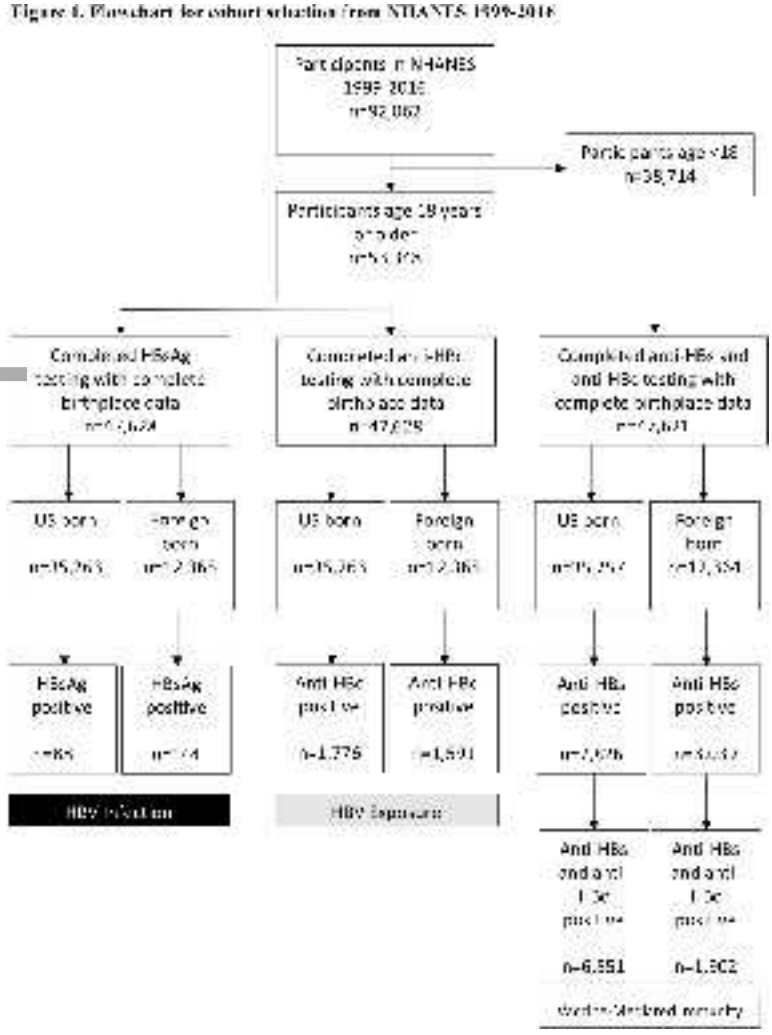
1-3	49.49 (41.95-57.106	55.44 (41.14-68.89)	45.01 (36.96-53.32)	
4-9	12.84 (9.06-17.89)	14.33 (8.32-23.57)	11.72 (7.50-17.85)	
10+	16.65 (10.46-25.47)	26.83 (15.28-42.72)	8.98 (4.51-17.08)	

*Data shown as population estimates derived from 232 infected persons, NHANES 1999-2016

[#]P-value represents the significant level of the comparison between U.S.-born and foreign-born HBV patients

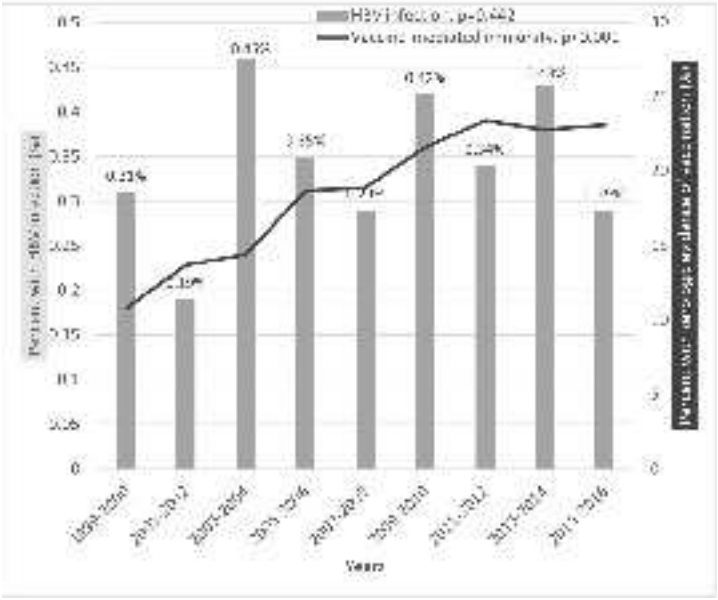
[##]NAFLD defined by USFLI, USFLI≥30

**Aspartate aminotransferase upper limit of normal: 40 U/L, Alanine aminotransferase upper limit of normal: 35 U/L for males 25 U/L for female



hep_30831_f1.tiff

Figure 2A: *Overall* - Trends in HBV infection (positive HBsAg) and vaccine-mediated immunity (positive anti-HBs with negative anti-HBc), 1999-2016



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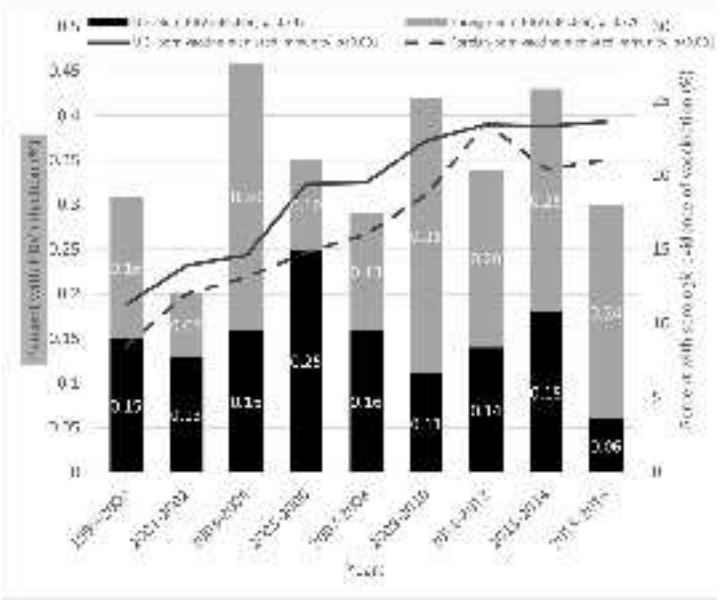
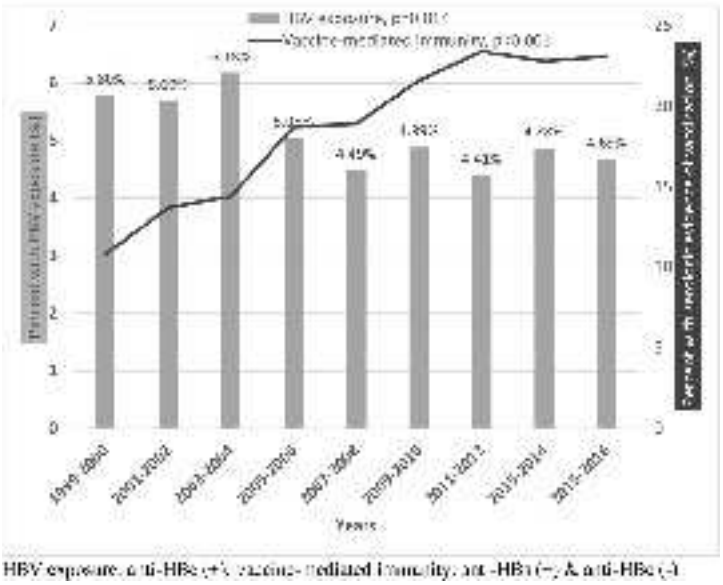


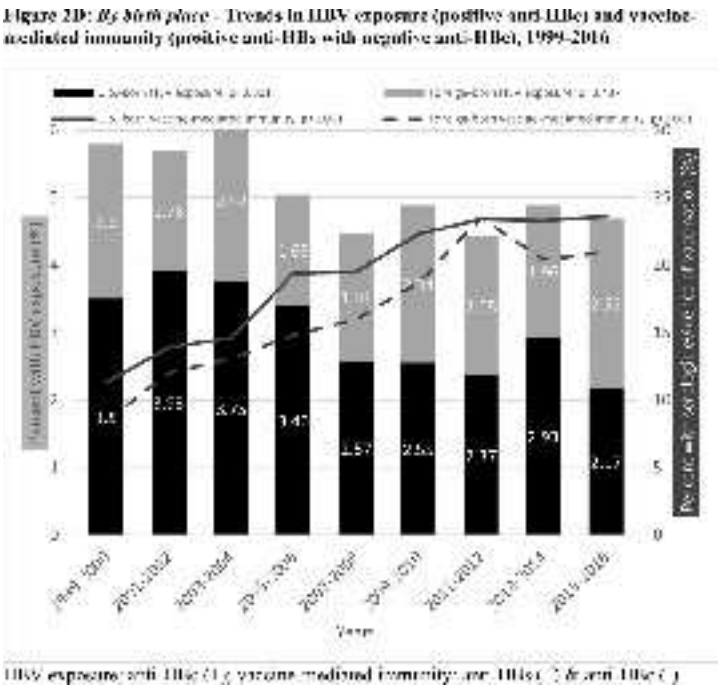
hep_30831_f2b.tiff

Figure 2C: Overall - Trends in HBV exposure (positive anti-HBc) and vaccine-mediated immunity (positive anti-HBs with negative anti-HBc), 1999-2016



HBV exposure: anti-HBc (+); vaccine-mediated immunity: anti-HBs (+) & anti-HBc (-)

hep_30831_f2c.tiff



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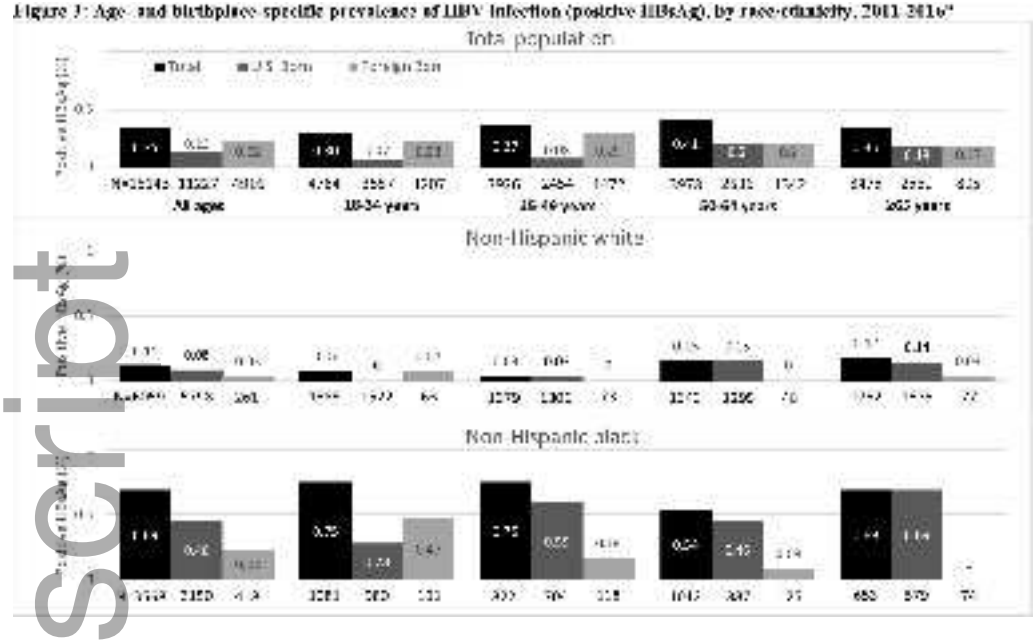

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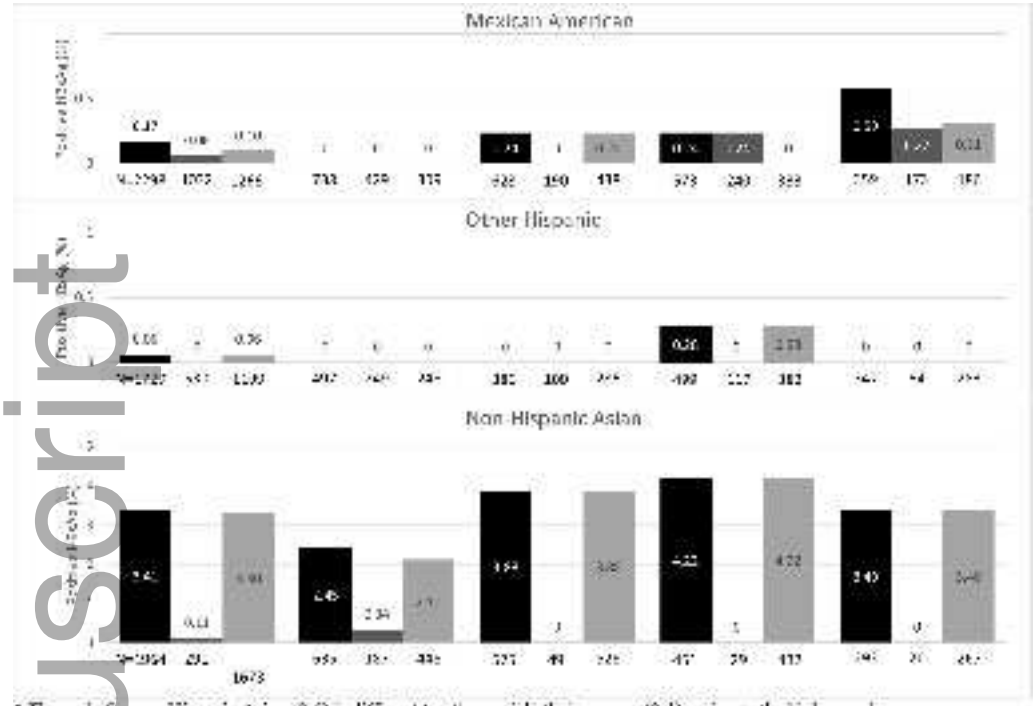
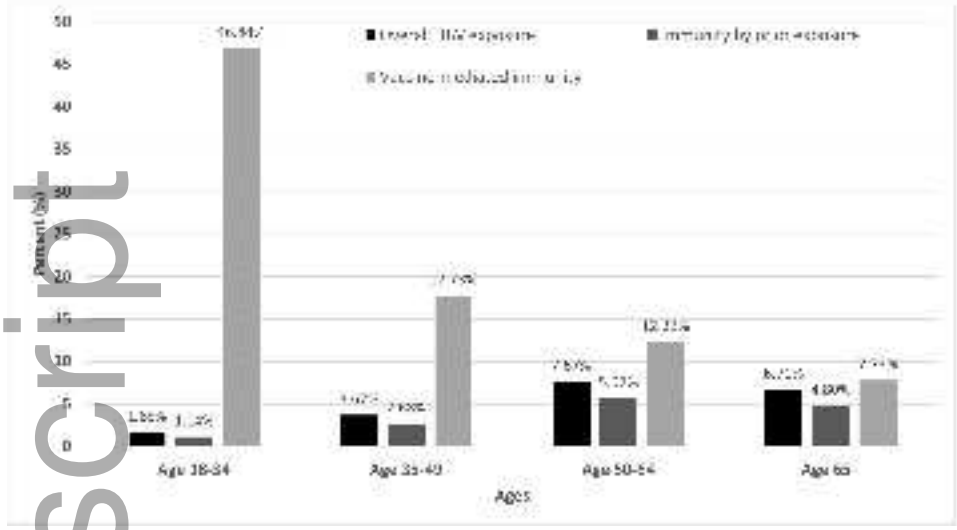


* The scale for non-Hispanic Asian (3-5) is different to other ethnicity groups (0-1) owing to the high prevalence

hep_30831_f3-2.tiff

Figure 4: Age-specific prevalence of overall HBV exposure (positive anti-HBc), immunity by prior exposure (positive anti-HBs and positive anti-HBc), and vaccine-mediated immunity (positive anti-HBs with negative anti-HBc), 2013-2016



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